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Brief Clinical Report

Ullrich-Turner Syndrome and Neurofibromatosis-1

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There is a well-known association between neurofibromatosis-1 (NF1) and Noonan syndrome-like manifestations, including short stature, short broad neck, and hypertelorism. These anomalies are thought to be due to variable expression of the NF1 gene. We report on two girls with NF1 who were found to have the Ullrich-Turner syndrome. Case 1, a 12-year-old white girl, was followed in a Neurofibromatosis Clinic because of multiple café-au-lait spots and a family history of NF1 in her mother and sister. On examination, she had short stature, hypertelorism, and short neck with low posterior hairline. Karyotype was 86% 46,XY/14% 45,X. Case 2, the first child of a woman with NF1, presented at birth with lymphedema of hands and feet and a short broad neck. Karyotype was 45,X. At age 23 months she was short, had epicanthic folds, hypertelorism, narrow palate, right simian crease, 19 café-au-lait spots, and axillary freckling. We conclude that chromosome studies should be performed in girls with NF1 who have short stature and Noonan- or Ullrich-Turner-like findings. Dilemmas raised by the dual diagnoses of NF1 and Ullrich-Turner syndrome include potential risks of growth hormone therapy and estrogen replacement therapy.

KEY WORDS: neurofibromatosis-1, Ullrich-Turner syndrome, Noonan syndrome, mixed gonadal mosaicism, growth hormone

INTRODUCTION

Neurofibromatosis-1 (NF1) is an autosomal dominant disorder with variable expression, manifesting with café-au-lait spots, axillary freckling, cutaneous neurofibromata, optic nerve gliomas, osseous abnormalities, and learning disabilities. The incidence is about 1/3,000 [Crowe et al., 1956]. Ullrich-Turner syndrome (UTS) is one of the more common chromosome disorders, with an incidence of about 1/5,000 liveborn infants [Thompson et al., 1991]. Affected girls have short stature, congenital lymphedema, widely spaced nipples, webbed neck, low posterior hairline, ovarian dysgenesis, and pigmented nevi. Noonan syndrome (NS) is a disorder which usually occurs sporadically but may be an autosomal dominant trait [Mendez and Opitz, 1985]. Frequent findings are short stature, epicanthic folds, hypertelorism, short or webbed neck, congenital heart defect, and mild mental retardation.

There have been multiple reports of an association between neurofibromatosis-1 and NS-like anomalies [Abuelo and Meryash, 1988; Allanson et al., 1985; Mendez, 1985; Opitz and Weaver, 1985; Shuper et al., 1987]. In both disorders patients may have short stature, short broad neck, and hypertelorism. Although it has been speculated that a separate "NF-Noonan syndrome" disorder exists [Opitz and Weaver, 1985], it is now thought that Noonan-like traits can be part of the variable phenotype of the NF1 mutation [Stern et al., 1992]. We are reporting on two girls with NF1 and Noonan-like anomalies, who were subsequently shown to have UTS on chromosome analysis.

CLINICAL REPORTS

Patient 1, a 12-year-old white girl, was followed in the Neurofibromatosis Clinic at Children's Hospital Medical Center because of multiple café-au-lait spots and a family history of NF1 in her mother, sister, and maternal grandmother. She was born at term with a BW of 2,960 g. She has had no major medical problems except for recurrent otitis media. She was an average student in school, with no evidence of learning disability. She had been noted on several previous visits to the NF Clinic to have "Noonan-like findings," which were attributed to variable expression of the NF1 gene. At her most recent visit, the family was concerned about

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her short stature, particularly since she was shorter than her younger sister who also had NF1.

On examination at 12 years, her height was 132 cm (<5th centile), weight was 35.9 kg (15th centile), and OFC was 54.5 cm (75th centile). There were no obvious Lisch nodules, but she had apparent mild hypertelorism, short neck without webbing, and a low posterior hairline (Fig 1). Cardiac status and abdomen were normal. Genitalia were normal. There were multiple nevi on the neck and back, and five café-au-lait spots over 0.5 cm diameter. There was no axillary or inguinal freckling, and no cutaneous neurofibromata. Dermatoglyphic analysis documented whorls of large pattern density on all ten finger tips. The atd angles were right palm 50° and left palm 46°. Both fourth interdigital spaces had a loop pattern. A large distal whorl was present on the right hypothenar area. A radial exit of main-line A was present on each palm. Dermatoglyphics were consistent with those seen in the UTS.

Fig. 1. Patient 1 at age 12 years. Note hypertelorism and short neck.

Chromosome studies were obtained from peripheral blood lymphocytes because of the UTS-like findings and showed mosaicism, 14% 45,X/ 86% 46,XY, consistent with mixed gonadal dysgenesis. Although we thought that this patient had NF1, she did not strictly meet the NIH Consensus Conference diagnostic criteria, as she had only five café-au-lait spots in addition to an affected 1st degree relative. Molecular linkage studies of the family performed at the University of Utah confirmed that patient 1 had with high likelihood inherited the NF1 allele. MRI of the brain showed a single focus of abnormal signal on T2 weighted images in the right temporal lobe, thought to be consistent with findings of NF1. Results of echocardiogram and renal ultrasound study were normal. A gonadectomy was performed because of the risk of gonadoblastoma related to mixed gonadal dysgenesis. Growth hormone therapy was considered for treatment of her short stature; however, as the safety of growth hormone in patients with neurofibromatosis is not documented, the family chose not to pursue this option.

Patient 2 is a biracial child who was the product of the first pregnancy of a 24-year-old woman who was diagnosed with NF1 during her pregnancy. Delivery was by emergency C-section, with a BW of 3,636 g. She was noted at birth to have multiple findings of UTS, including puffy hands and feet, apparently short neck with redundant skin folds, shield-shaped chest, and a single simian crease. No café-au-lait spots were noted at birth. Karyotype from a culture of peripheral blood lymphocytes was 45,X in all cells examined. On examination at age 2 weeks, she was noted to have four small café-au-lait spots; on re-examination at 23 months, she had developed additional café-au-lait spots and appeared to be making normal developmental progress.

At 23 months, her weight was 10.0 kg (35th centile), length was 77 cm (<5th centile; 50th centile on UTS growth chart), and OFC was 48 cm (50th centile). She had epicanthic folds with apparent hypertelorism, flat nasal bridge, apparently low-set ears, downturned mouth, and a short broad neck (Fig. 2). Cardiac status was normal. There were 19 café-au-lait spots over 0.5 cm diameter, and several axillary freckles. There were no cutaneous neurofibromata. Results of an echocardiogram and renal ultrasound study were normal. MRI of the brain at 12 months of age showed a small focus of increased signal in the right middle cerebellar peduncle, thought to be consistent with NF1.

DISCUSSION

Our report of two girls with NF1 and apparent Noonan-like manifestations who were subsequently shown to have UTS, emphasizes the need to perform chromosome analysis in girls with NF1 who present with short stature and a NS-like phenotype. We are aware of only one other published report of the co-occurrence of NF-1 and UTS, in a fetus diagnosed prenatally with NF-1 based on linkage studies and a karyotype of 45,X [Upadhyaya et al., 1992]. We presume that the presence of both disorders in these patients was a chance occurrence of two relatively common genetic disorders. We cannot speculate on any process that would make

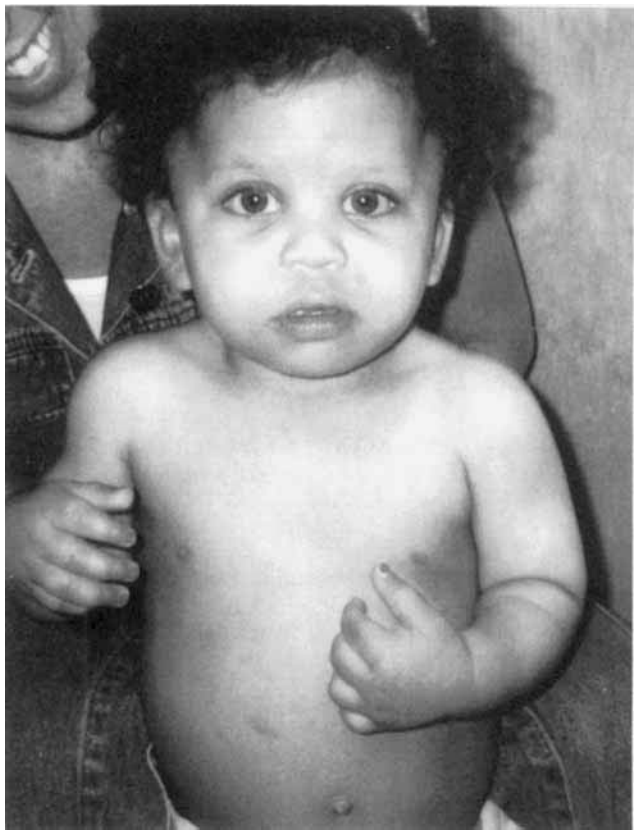

Fig. 2. Patient 2 at age 23 months. Note hypertelorism, epicanthic folds, flat nasal bridge, apparently low-set ears, downturned mouth, short broad neck, and café-au-lait spots.

patients with NF-1 more likely to have UTS, or vice versa. In fact, the cause of UTS in our two patients was different, being due to somatic mosaicism in case 1, and presumed meiotic nondisjunction in case 2.

Several authors have recently reported large deletions of the NF1 gene in patients who have minor facial anomalies and severe manifestations of NF1 [Leppig et al., 1994; Wu et al., 1995; Kayes et al., 1994]. In light of these findings, FISH studies for NF1 deletions may also be appropriate to perform in NF1 patients who present with minor anomalies.

Our experience with these patients raises the issue of efficacy and safety of growth hormone therapy for treatment of short stature in girls who have NF1 and UTS. Growth hormone therapy is now considered a treatment for short stature in UTS and results in increased adult height [Rosenfeld et. al., 1988]. The risk of increased tumor growth or other complications related to growth hormone therapy in patients with NF-1 has not been well studied, and there is little information available in the medical literature. Additional information is also needed on what risks, if any, there may be from estrogen replacement therapy for these patients.

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